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Transanal Total Mesorectal Excision for Adult Patients with Rectal Cancer: A Review of Clinical Effectiveness and Cost-Effectiveness

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Authors: Tasha Narain, Kendra Brett, Lory Picheca

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Abbreviations

CRM	Circumferential resection margin
DRM	Distal resection margin
EQ-5D-3L	Euroquol group five dimensions three levels
IPSS	International Prostate Syndrome Score
LARS	Low Anterior Resection Syndrome
LaTME	Laparoscopic total mesorectal excision
RCT	Randomized control trial
SR	Systematic review
SSI	Surgical site infections
TaTME	Transanal total mesorectal excision
TME	Total mesorectal excision
MA	Meta analysis

Context and Policy Issues

Colorectal cancer is the third most commonly diagnosed cancer in Canada.[1] In 2019 in Canada, colorectal cancer made up 13% of cancer cases in males, and 11% of cancer cases in females.[1] Rectal cancer is a subset of colorectal cancer, and symptoms include changes in bowel habits, rectal bleeding, and weight loss.[2] The treatment of rectal cancer can be challenging as what works for one patient may not work for another, additionally the five year survival of patients with advanced rectal cancer is 58%.[3] The location of rectal cancer is defined by its distance from the anal verge (i.e., the junction of the anal canal and the external skin); lower or distal cancers are four to eight centimetres from the anal verge, middle rectal cancers are eight to 12 centimetres, and upper or proximal cancers are 12 to 15 centimetres from the anal verge.[4]

Surgery is one of the main therapies for rectal cancer, with the primary goal being complete removal of the tumour.[4] The stage, size, and location of the tumour, and the patient's characteristics (e.g., sex, BMI, skeletal morphology) can affect the choice of surgical approach for rectal cancer.[4]

Total mesorectal excision (TME), which involves the complete removal of the rectum and surrounding lymphatic tissue,[5] is the standard of care for tumours in the distal to middle rectum.[4] TME can be performed with open or laparoscopic techniques.[2] Laparoscopic TME (LaTME) can be complicated by certain factors, such as the patient's pelvic anatomy (i.e., a narrow pelvis),[5] or obesity, thus reducing the surgeon's ability to access the distal part of the rectum.[6] In such cases, a laparoscopic procedure would need to be converted to the more invasive open TME procedure, which may result in worse short-term post-surgical outcomes.[2]

Transanal endoscopic surgery is a technique that offers access to rectal cancers through the anus.[7] Transanal total mesorectal excision (TaTME), is a surgical procedure that

combines the transanal endoscopic surgery approach with the LaTME procedure. TaTME facilitates the surgical treatment for distal and middle rectal cancers; the distal part of the rectum can be reached through the transanal approach, and the tumours in the middle rectum can be reached laparoscopically.[4] The TaTME approach is a minimally invasive surgery for rectal cancer, and may facilitate access to tumours that are not amenable to the laparoscopic approach (e.g., patients who are obese, patients who have a narrow pelvis).[4]

In some Canadian hospitals, both the TME and the transanal endoscopic surgery are regularly used for rectal cancer, however, the TaTME procedure which combines both approaches is not widely used. The purpose of the report is to review and critically appraise the evidence pertaining to the clinical effectiveness and the cost-effectiveness of the TaTME for adult patients with middle to distal rectal cancer compared to open and laparoscopic TME. This information may be use used to inform decision making relating to clinical practice for the use of TaTME.

Research Questions

1. What is the clinical effectiveness of Transanal Total Mesorectal Excision for adult patients with rectal cancer?
2. What is the cost-effectiveness of Transanal Total Mesorectal Excision for adult patients with rectal cancer?

Key Findings

There is strong evidence based on five high-to-moderate quality systematic reviews and six moderate-to-low quality non-randomized studies that suggests that Transanal Total Mesorectal Excision is clinically effective and safe for patients with rectal cancer based on the assessment of short-term outcomes when compared to Laparoscopic Total Mesorectal Excision.

Limited evidence from two non-randomized trials was insufficient to be make statements regarding the clinical effectiveness of Transanal Total Mesorectal Excision compared with Open Total Mesorectal Excision based on the assessment of short-term outcomes.

Insufficient evidence regarding long-term clinical effectiveness was identified for Transanal Total Mesorectal Excision for adult patients with rectal cancer compared to Open or Laparoscopic Total Mesorectal Excision. Conclusions based on comparative long-term clinical effectiveness cannot be made.

No evidence regarding the cost-effectiveness of Transanal Total Mesorectal Excision for adult patients with rectal cancer was identified in comparison to open or Laparoscopic Total Mesorectal Excision.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE All via Ovid, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search

strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were rectal neoplasms and transanal total mesorectal excision. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and March 25, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult patients with mid to distal rectal cancer. Exclude patients with anal cancer
Intervention	Transanal Total Mesorectal Excision (TaTME) (hybrid of transanal endoscopic microsurgery and laparoscopy)
Comparator	Open or Laparoscopic Total Mesorectal Excision
Outcomes	Q1: Clinical effectiveness: Conversion to open procedure, peri-operative morbidity, readmission, length of stay, recurrence of cancer (locoregional or systemic), disease-free survival, circumferential resection margin, positive margin; Adverse events (e.g., infection, anastomotic leak, incisional hernia, injury to the urethra, bladder, iliac, complication rate), Q2: Cost-effectiveness
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and economic evaluations

TaTME = Transanal Total Mesorectal Excision.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2015. Primary studies that were captured in an included SR were excluded, unless relevant outcomes or comparators from the primary studies were not fully reported in the systematic reviews. SRs with full overlap (i.e., the included studies are fully captured in another more recent or more comprehensive SR) were excluded.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised by one reviewer using AMSTAR II[8] and non-randomized studies were critically appraised using the Downs and Black checklist.[9] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 478 citations were identified in the literature search. Following screening of titles and abstracts, 436 citations were excluded and 41 potentially relevant reports from the electronic search were retrieved for full-text review. There were no potentially relevant

publications from the grey literature search. Of these potentially relevant articles, 28 publications were excluded for various reasons, and 13 publications met the inclusion criteria and were included in this report. These comprised 5 systematic reviews and 8 non-randomized studies. Two of the included non-randomized retrospective studies[10,11] were included in two systematic reviews.[12,13] These were included separately as results from specific treatment arms (TaTME versus open TME) were not reported in the systematic reviews. Appendix 1 presents the PRISMA[14] flowchart of the study selection.

Summary of Study Characteristics

Five SRs with meta-analysis[12,13,15-17] and eight non-randomized studies[10,11,18-22] were identified and included in this report. Detailed characteristics are available in Appendix 2, Table 2 and Table 3.

Study Design

This report included five SRs with meta-analysis[12,13,15-17] published between 2016 and 2020 that examined the comparative efficacy of TaTME compared with LaTME for patients with mid to low rectal cancer. Three SRs included both RCTs and observational primary studies,[13,15,16] while two SRs included observational studies.[12,17] The SRs included literature published prior to November 2019,[13] December 2018,[12] February 2017,[15] November 2015,[16] and March 2016.[17] Overlap in the primary studies included was observed across all SRs. Additional details regarding overlap are provided in Appendix 5.

This report included eight non-randomized studies published between 2018 and 2020, which included between 48 and 261 patients. Six studies were single center[10,11,18-20,22] (where four studies had overlapping populations).[11,18-20] One study was a subgroup analysis of a prospective cohort study.[23] Seven studies were retrospective cohorts (with one study using data generated from a RCT[21] and five studies including prospective outcome assessments[11,18-20,22]).

Country of Origin

One SR was led by authors in the United Kingdom.[13] Four SRs were led by authors in China.[12,15-17] Four non-randomized studies were conducted in Denmark,[11,18-20] two were conducted in the Netherlands,[22,23] one was conducted in Taiwan,[10] and one in China.[21]

Patient Population, Interventions and Comparators

All five SRs included patients with low or mid rectal cancer who were treated with TaTME or LaTME.[12,13,15-17] Six non-randomized studies assessed patients with low or mid rectal cancer who were treated with TaTME or LaTME.[18-22] Two non-randomized studies examined patients with low or mid rectal cancer who were treated with TaTME or Open TME. [10,11]

Outcomes

All five SRs and eight non-randomized studies comparing treatment with TaTME to LaTME or open TME reported various oncological, intraoperative, and postoperative outcomes.

Outcomes relevant to the selection criteria were the focus of this review. Five SRs[12,13,15-17] and two non-randomized studies[11,21] assessed completeness or quality of the mesorectum. Circumferential resection margin (CRM) and positive CRM were assessed in five SRs.[12,13,15-17] CRM distance was assessed in one non-randomized study,[20] while CRM

involvement (CRM positive) was assessed in three non-randomized studies.[11,20,21] The CRM is the surgical area created by dissection during removal of the rectum from the surrounding tissue.[5] It is a non peritonized, bare area of resection sample.[5] Positive CRM is defined as a tumor extension or the presence of positive lymph nodes <1 mm from the radial, non peritonealized soft tissue border. [5,24] Patients who have an edge <1mm have an increased risk of distant metastases, therefore a positive CRM is indicative of poorer prognosis.[5,24,25] Distal resection margin (DRM) was assessed in five SRs[12,13,15-17] and four non-randomized studies,[10,11,20,21] while positive DRM was assessed in three SRs[12,15,16] and three non-randomized studies.[11,20,21] The DRM is the distance between the tumor to the distal cut edge of the tissue;[11,25] in most recent studies, DRM is considered positive when ≤ 1 mm.

Length of hospital stay was reported in four SRs[12,15-17] and four non-randomized studies.[10,11,21,23] Readmission was assessed in four SRs[12,15-17] and two non-randomized studies.[11,23] Reoperation was assessed in two non-randomized studies.[21,23] Conversion to open TME was assessed in five SRs[12,13,15-17] and three non-randomized studies.[20,21,23]

Intraoperative complications were assessed in five SRs[12,13,15-17] and two non-randomized studies.[10,23] Post-operative complications were assessed in five SRs[12,13,15-17] and one non-randomized study. [21] Anastomotic leak was assessed in five SRs[12,13,15-17] and three non-randomized studes.[10,21,23] Ileus was assessed in three SRs[12,15,16] and one non-randomized study.[10] Blood loss was assessed in three SRs[12,15,17] and three non-randomized studies.[10,20,21] Urinary morbidity was assessed in two SRs.[12,16] In male patients, urinary function was assessed using International Prostate Syndrome Score (IPSS) in two studies.[18,22] Perforation was assessed in one non-randomized study.[20] One study assessed internal sphincter damage by measuring resting pressure and the external anal pressure by measuring squeeze pressure.[19] Bowel dysfunction assessed through total Low Anterior Resection Syndrome (LARS) was examined in three non-randomizes studies.[18,19,22] Surgical site infections (SSIs)[13] were assessed in one SR and wound infections were assessed in one non-randomized study.[23] Local cancer recurrence was assessed in one SR[12] and one non-randomized study, although timeframes for recurrence were not specified.[10]

Mortality assessed 30 days post operation was reported in two non-randomized studies,[10,21] and assessed in one non-randomized study with no time-frame specified.[21] Two-year disease free survival rate was reported in one non-randomized study.[10]

Quality of life was assessed using the EORTC QLQ-C30 in two studies[18,22] and the Euroquol group five dimensions three levels (EQ-5D-3L) in one study.[22]

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Systematic Reviews and Meta-Analyses

All included SRs had few limitations and were generally well conducted. Based on the AMSTAR 2 assessment of five SRs, all SRs had well described research questions and inclusion criteria. One SR had a published protocol,[13] it is unclear if the other four SRs had methods established a priori as no pre-published protocol was referenced in the publication. All SRs except one[17] included clear statements regarding the use of PRISMA statement standards for the conduct of the SR and MA.

All SRs searched multiple databases and performed the study selection and data extraction using two reviewers. Discrepancies were resolved by consensus[15-17] or by a third reviewer[13] in all but one SR,[12] where the method of resolution was not reported. All SRs assessed the quality of included studies using the Newcastle-Ottawa scale, one SR assessed the quality of included RCTs through the use of the Cochrane Library Handbook 5.1.0.[15] All SRs assessed between-study heterogeneity using Cochran's Q test with I^2 reported. Clear criteria for the selection of a random or fixed-effect models for MAs were provided in four SRs.[13,15-17] Random-effect MAs were performed in one SR with no clear rationale provided for the use of random-effect MAs compared with fixed-effect MAs.[12]

Publication bias was assessed based on visual inspection of funnel plots in all SRs. Three SRs included both RCTs primary studies,[13,15,16] while two SRs were limited by only including observational studies.[12,17] None of the studies included long-term outcomes. In three SRs the authors reported not having a conflict of interest,[15-17] the remaining two SRs did not provide a statement on conflict of interest.

Non-Randomized studies

All eight non-randomized studies had clear descriptions of the objectives, patient eligibility criteria, interventions and controls.[10,11,18-22] Baseline characteristics were generally sufficiently reported and well balanced between arms. Follow-up time was not reported either at all or by treatment arm in four non-randomized studies.[11,20,21,23] In the remaining studies where follow-up time was reported, it was consistently significantly shorter for the TaTME arm compared to the LaTME or open TME arm. A rationale for this difference was specified in some studies which attributed it to the hospitals changing procedures over the retrospective period as the more novel TaTME procedure became preferable. Despite this rationale, differential follow-up introduces the potential for bias.

In two studies, there were significantly fewer lymph node-positive patients in the TaTME group.[18,19] In one study, there were fewer patients with stage I cancer in the open TME group compared with the TaTME group. The implication of the differences in these baseline characteristics by treatment group is unclear, especially since most if not all of the outcomes assessed were short-term.[10] It is possible that these differences may be of more relevance with the assessment of longer-term outcomes such as disease-free status or relapse, however long-term outcomes were not the focus of these studies. The non-randomized studies were generally limited by their absence of long-term efficacy and safety outcomes. Only one study reported two-year disease-free survival rate.[10]

Generally, the methodology used across the non-randomized studies was appropriate. However, in all studies it was unclear if analysts were blinded to the treatment status. Additionally, across all studies it is unclear if a power calculation was performed to determine sample size, and thus if the study was powered to detect a statistical difference between treatment arms. In one study, it was clear that no power calculation had been performed as it was a subgroup within a larger study.[23]

The number of surgeons performing the procedures for TaTME, LaTME, and open TME were not consistently reported. When the number of surgeons was reported, often there were more surgeons performing LaTME and open TME compared with TaTME. The experience level of surgeons was not specified in any of the studies. The differences in the experience level and number of surgeons are likely to be a source of heterogeneity.

Summary of Findings

A detailed summary of findings and author's conclusions are provided in Appendix 4. All SRs had substantial overlap in primary studies. Details regarding SR overlap are provided in Appendix 5. The results from specific treatment arms (TaTME versus open TME) were included from two non-randomized retrospective studies, [10,11] data from these studies pertaining to the comparison between TaTME and LaTME is already included in two of the reviewed SRs.[12,13]

Clinical effectiveness of Transanal Total Mesorectal Excision for adult patients with rectal cancer

Completeness/quality of mesorectal excision

Three SRs determined that the macroscopic quality of the mesorectum was significantly better in the TaTME group than in the LaTME group.[15-17] Between-study heterogeneity was not significant in these SRs. Two SRs and one non-randomized study found no statistically significant difference in the macroscopic quality of the mesorectum between TaTME and LaTME.[12,13,21] In the comparison between TaTME and open TME, one non-randomized study found no statistically significant difference in the specimen quality.[11]

Circumferential resection margin

Three SRs found that the CRM was statistically significantly longer with TaTME compared to LaTME in three SRs. [15-17] Between-study heterogeneity was not significant in these SRs. Two SRs[12,13] and one non-randomized study[20] found no statistically significant difference between TaTME and LaTME in CRM. When compared categorically, one non-randomized study found a longer CRM associated with TaTME compared to open TME[10] while another non-randomized study reported CRM results descriptively.[11]

Positive circumferential resection margin

TaTME was associated with a significantly lower rate of positive CRM compared to LaTME. [13,15-17] Between-study heterogeneity was not significant in these SRs. One SR[12] and two non-randomized studies[20,21] found no statistically significant difference in positive CRM between TaTME and LaTME. For the comparison between TaTME and open TME, one non-randomized study found no statistically significant difference.[11]

Distal resection margin

No statistically significant difference in the length of DRM was found between TaTME and LaTME based on the findings from five SRs[12,13,15-17] and one non-randomized study[21], while a single non-randomized study determined that TaTME was associated with a statistically significantly longer DRM than LaTME.[20] For the comparison between TaTME and open TME, one non-randomized study[11] found no statically significant difference in DRM, and one non-randomized study reported the results descriptively.[10]

Positive distal resection margin

Based on the findings from three SRs[12,15,16] and two non-randomized studies[20,21] positive DRM was not statically significantly different for TaTME compared to LaTME. One study compared positive DRM for TaTME and open TME descriptively.[11]

Length of hospital stay

Four SRs[12,15-17] and two non-randomized studies[21,23] found no statistically significant difference in length of stay between TaTME and LaTME. For the comparison between TaTME and open TME, one non-randomized study found TaTME to have a statistically significant shorter length of post-operative hospital stay compared with open TME[11], while another non-randomized study[10] reported this outcome descriptively.

Readmission

Four SRs[12,15-17] and one non-randomized study[23] found no statistically significant difference in remission between TaTME and LaTME. Readmission was assessed descriptively by one non-randomized study and suggested no difference between TaTME to open TME.[11]

Reoperation

No statistically significant difference in reoperation was found for the comparison of TaTME with LaTME based on the results of two non-randomized studies.[21,23]

Conversion to open procedure

Evidence from three SRs[13,15,16] determined that TaTME was associated with a significantly lower rate of conversion to an open procedure compared to LaTME. Between-study heterogeneity was not significant across these SRs. Two SRs and three non-randomized studies[20,21,23] found no statistically significant difference between TaTME and LaTME for conversion to open procedure.[12,17]

Complications

All five SRs found no statistically significant difference in the occurrence of intraoperative complications between TaTME and LaTME.[12,13,15-17] Peri-operative complications were reported descriptively in two non-randomized studies comparing TaTME and open TME reported descriptively and suggested no differences between treatments. [10,11]

One SR determined that the TaTME group showed a significantly lower rate of postoperative complications than the LaTME group.[16] Four SRs[12,13,15,17] and one non-randomized study[21] found no statistically significant difference in the occurrence of postoperative complications between TaTME and LaTME.

One non-randomized study found no statistically significant difference between TaTME and LaTME in the occurrence of complications based on the Comprehensive Complication Index.[23]

Anastomic Leak

Five SRs and one non-randomized study[23] found no statistically significant difference in the occurrence of anastomic leak between TaTME and LaTME.[12,13,15-17] Anastomic leak was reported descriptively in a single non-randomized study for the comparison of TaTME with LaTME[21] and open TME[10] and suggested no difference.

Ileus

Three SRs found no statistically significant difference in ileus between TaTME and LaTME.[12,15,16] Descriptive evidence from one non-randomized study suggested no difference in ileus.[10]

Blood loss

Three SRs[12,15,17] and one non-randomized study[21] found no statistically significant difference in blood loss between TaTME and LaTME, while one non-randomized study found significantly greater blood loss associated with LaTME.[20] Open TME was associated with significantly more blood loss compared to TaTME based on the findings from a single non-randomized study.[10]

Urinary morbidity

Two SRs found no statistically significant difference in urinary morbidity between TaTME and LaTME.[12,16] In male patients, urinary function was assessed using International Prostate Syndrome Score (IPSS) in two studies where no statistically significant difference was reported between TaTME and LaTME.[18,22] Urinary morbidity was reported descriptively in a single non-randomized study that suggested no difference between TaTME with open TME. [10]

Perforation

No statistically significant difference in perforation found between TaTME and LaTME based on results from one non-randomized study.[20]

Sphincter Damage

One non-randomized study found no statistically significant difference in sphincter damage between TaTME and LaTME based on assessments of resting pressure and squeeze pressure.[19]

Bowel Dysfunction

Three non-randomized studies found no statistically significant difference in bowel dysfunction between TaTME and LaTME.[18,19,22]

Surgical site infections

One SR found no statistically significant difference in the occurrence of SSIs between TaTME and LaTME.[13] One non-randomized study found no difference in wound infection between TaTME and LaTME. [23]

Recurrence of cancer

One SR[12] found no statistically significant difference in local recurrence of cancer between TaTME and LaTME. One non-randomized study reported local recurrence of cancer descriptively and suggested no difference between TaTME and open TME.[10]

Mortality

Mortality assessed 30 days post operation was not significantly difference between TaTME and LaTME based on results from one non-randomized study,[23] this finding was supported by descriptive results from a second non-randomized study.[21] No statistically significant difference in mortality was reported between TaTME and open TME.[10]

Disease-Free Survival

Two-year disease-free survival rate was statistically significantly longer for TaTME compared to open TME based on results from one non-randomized study.[10]

Health Related Quality of Life

HrQoL was assessed was not statistically significantly different between TaTME and LaTME based on results from two non-randomized studies. [18,22]

Cost effectiveness of Transanal Total Mesorectal Excision for adult patients with rectal cancer

No relevant evidence regarding the cost effectiveness of TaTME compared with open or LaTME for adult patients with rectal cancer was identified; therefore, no summary can be provided.

Limitations

The majority of evidence supporting the SRs was derived from observational studies. Three SRs contained RCTs in their included studies, and at most they accounted for three of the included primary studies. The limited inclusion of RCTs reduces the quality of evidence as observational studies are subject to biases and are potentially impacted by confounding.

The SRs were strongly focused on short term outcomes. One SR and two non-randomized studies provided information on cancer recurrence, however the timeframe for this outcome was limited to 30 days. One non-randomized study provided two-year disease-free survival data. More robust data on cancer recurrence as well as data on survival are needed. There was also an absence of data on long-term safety outcomes.

Inconsistency between the results of the SRs was observed and may present challenges to interpretation as there was substantial overlap in the primary studies; however none of the results were in direct opposition of each other (i.e., statistically significant positive association compared to a negative association). While substantial overlap in included primary studies was present, one possible explanation for inconsistency may relate to the range in number of primary studies (N=7 to N=18).

Heterogeneity in several of the non-randomized studies was identified. Heterogeneity often pertained to differential length of follow-up, and differential number of surgeons who performed the procedures. In some non-randomized trails, information pertaining to follow-up and number of surgeons was not reported. None of the SRs or non-randomized studies reported on the level of experience of surgeons. Surgeons with more experience may have better outcomes, however if experience is differential, it is likely to contribute to heterogeneity. One SR[17] provided information on length of follow-up by primary study when it was available (two out of seven primary studies), the other SRs did not report length of follow-up. The limited data on follow-up prevents strong conclusions from being made based on comparability of the treatment arms.

None of the SRs, primary studies within the SRs, or non-randomized studies were conducted by authors in Canada. It is unclear if the results of the SRs and non-randomized studies are generalizable to Canadian clinical practice.

None of the SRs provided comparative data between TaTME and open surgery. Limited comparative evidence was identified in two non-randomized studies, however due to the absence of high-quality data, conclusions cannot be made.

None of the literature provided relevant evidence regarding the cost effectiveness of TaTME compared with open or LaTME for adult patients with rectal cancer.

Conclusions and Implications for Decision or Policy Making

This report was comprised of five SRs[12,13,15-17] and six non-randomized studies[18-22] which explored the comparative clinical effectiveness of TaTME compared to LaTME for adult patients with rectal cancer. Evidence from two non-randomized studies regarding the comparative clinical effectiveness of TaTME compared to open TME was also included in this report.[10,11]

There is strong evidence that suggests that Transanal Total Mesorectal Excision is as clinically effective and safe as compared with Laparoscopic Total Mesorectal Excision for patients with rectal cancer based on the assessment of short-term outcomes, however there is insufficient data to conclude that TaTME is more clinically effective than LaTME. Evidence of comparable clinical effectiveness between TaTME and LaTME is supported by five high to moderate quality SRs. Collectively, the SRs had few limitations which mainly pertained to the incorporation of limited data from RCTs and failure to include relevant long-term outcomes. The results of the SRs were generally supported by six moderate-to-low quality non-randomized studies. Further research incorporating evidence from randomized control trials, as well as evidence pertaining to long-term outcomes is needed to reduce uncertainty regarding the comparative efficacy of TaTME compared to LaTME for adult patients with rectal cancer.

Limited evidence from relevant comparators in two non-randomized trials was summarized and appraised in this report to provide insight into the comparison between TaTME and open TME. However, given the state of evidence, further research incorporating evidence from high quality studies and systematic reviews is needed before conclusions can be made regarding the comparative efficacy of TaTME compared to open TME for adult patients with rectal cancer.

Finally, conclusions cannot be made regarding the cost-effectiveness of Transanal Total Mesorectal Excision for adult patients with rectal cancer as no relevant evidence was identified in this review.

Based on the evidence available it is reasonable to expect that TaTME may be an effective and safe alternative to LaTME for the treatment of patients with rectal cancer.

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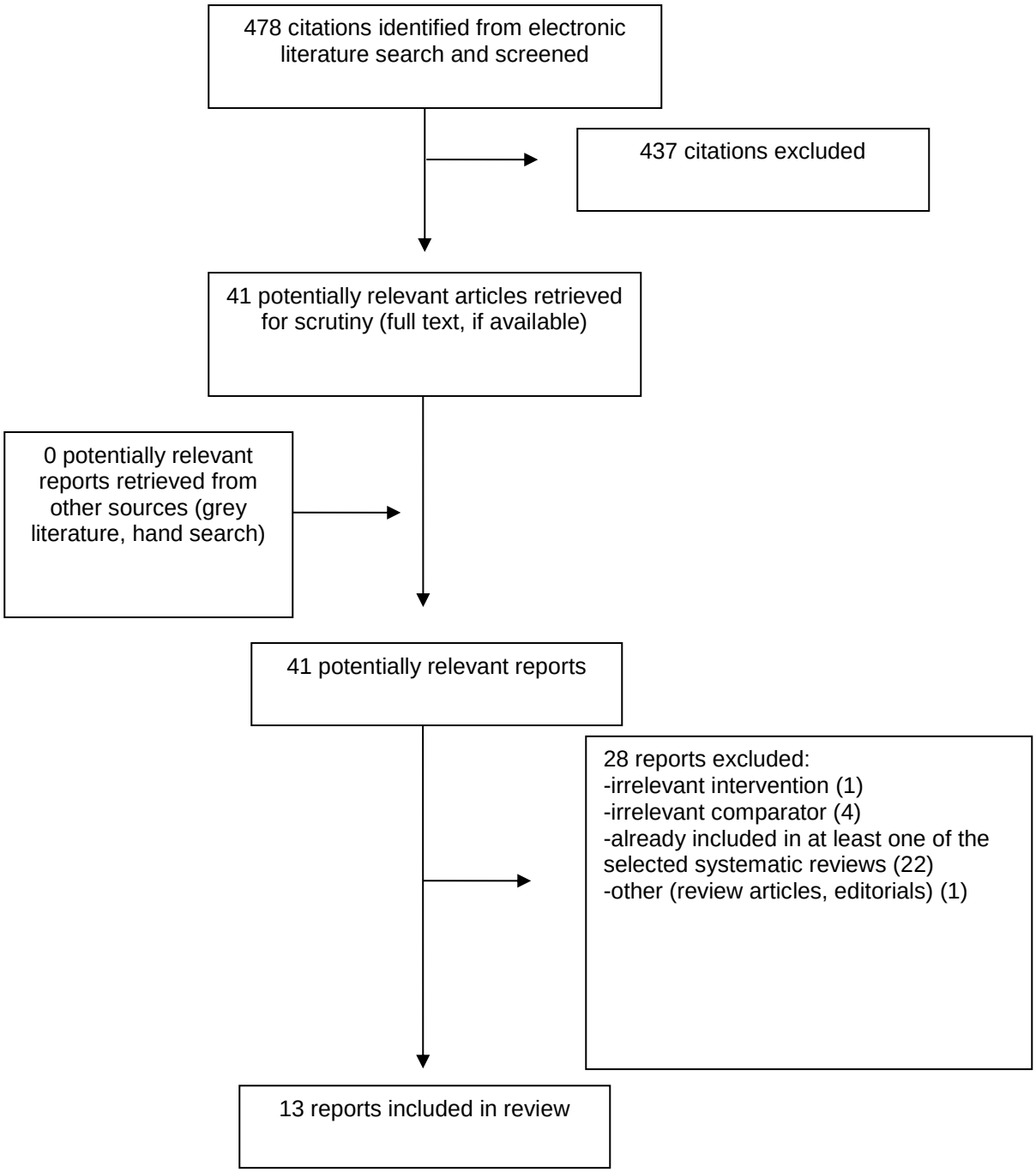
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 1: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Literature Searched, Numbers of Primary Studies Included, and Objective	Eligibility criteria	Intervention and Comparators	Clinical Outcomes
Hajibandeh, 2020[13] **UK**	**Search:** Databases searched included MEDLINE, EMBASE, CINAHL, CENTRAL (last search was performed November 1, 2019) **Included Studies:** 1 RCT 17 retrospective observational studies **Objective:** To evaluate comparative outcomes of TaTME and LaTME in patients with rectal cancer	**Inclusion criteria:** Adult patients (>18) with low or middle rectal cancer who underwent TaTME or LaTME **Exclusion criteria:** none specified	**Intervention:** TaTME **Comparator:** LaTME	**Outcomes:** Overall postoperative complications, anastomotic leak, SSIs, completeness of mesorectal excision, R0 resection, DRM, CRM, number of harvested lymph nodes, procedure time
Lin, 2019[12] **China**	**Search:** Databases searched included PubMed, Embase and the Cochrane Library databases (2008 to December 2018) **Included Studies:** 12 observational studies **Objective:** To assess and compare the short-term outcomes of TaTME with conventional LaTME for middle and low rectal cancer.	**Inclusion criteria:** RCTs and retrospective studies comparing TaTME with LaTME **Exclusion criteria:** lackof the sufficient data or outcomes of interest; duplicate publication; non-comparative studies, editorials, letters, conference abstracts, review articles, case reports and animal experimental studies; studies included high rectal cancer and abdomino-perineal resection	**Intervention:** TaTME **Comparator:** LaTME	**Outcomes:** estimated blood loss, operative time, conversion rate, intraoperative complications, overall postoperative complications, anastomotic leakage, ileus, urinary morbidity, reoperation, readmission rate, and length of hospital stay, quality of mesorectum, CRM, positive CRM, DRM, positive DRM, harvested lymph nodes and local recurrence
Hu, 2018[15] **China**	**Search:** Databases including PubMed, Embase, Web of Science, the Cochrane Library (from inception to Feb 15, 2017)	**Inclusion Criteria:** patients diagnosed with rectal cancer based on pathological examination; comparison of TaTME with LaTME	**Intervention:** TaTME **Comparator:** LaTME	**Outcomes:** harvested lymph nodes, CRM, positive CRM, DRM, positive DRM, conversion,

First Author, Publication Year, Country	Literature Searched, Numbers of Primary Studies Included, and Objective	Eligibility criteria	Intervention and Comparators	Clinical Outcomes
	Included Studies: 3 RCTs 10 matched case-control **Objective:** to compare TaTME and LaTME in terms of the oncologic and perioperative outcomes of patients with mid and low-rectal cancer in order to provide clinical reference.	for rectal cancer; reporting of the major outcome indicators **Exclusion Criteria:** reviews, meta-analysis, letters, case reports or conference abstracts; duplicate or repeat studies; studies on transanal extraction of other large bowel segments; non-human research		operation time, blood loss, ileus, mobilization of the splenic flexure, hospital stay, intraoperative complications, postoperative complications, and macroscopic quality of the mesorectum
Ma, 2016[16] **China**	**Search:** Databases searched included PubMed, Embase and the Cochrane Database (from January 2010 to November 2015). **Included Studies:** 1 RCT 6 matched case-control **Objective:** To compare the oncological and perioperative outcomes of TaTME and LaTME for patients with mid- and low-rectal cancer.	**Inclusion Criteria:** Patients with rectal cancer who received TaTME or LaTME. RCTs, cohort, and matched case-control trials with a sample size greater than 20 **Exclusion Criteria:** No LaTME control group, absence of outcomes of interest, duplicate publications or provision of insufficient data	**Intervention:** TaTME **Comparator:** LaTME	**Outcomes:** Macroscopic quality of mesorectum, harvested lymph nodes, DRM, CRM, positive CRM, operative time, conversion, hospital stay, mobilization of splenic flexure, intraoperative complications, postoperative complications, anastomotic leakage, ileus, urinary morbidity, readmission
Xu, 2016[17] **China**	**Search:** Databases searched included PubMed, Embase and the Cochrane Database (from Inception to March 19, 2016). **Included Studies:** 7 studies Objective: To evaluate the feasibility, safety, and	**Inclusion Criteria:** Diagnosis of rectal cancer was made based on pathological examination; published studies comparing TaTME with LaTME for rectal cancer; investigated the association of sufficient data **Exclusion Criteria:** letters, case reports, reviews, meta-	**Intervention:** TaTME **Comparator:** LaTME	**Outcomes:** CRM, positive CRM, distal margin distance, harvested lymph nodes, quality of TME, conversion, intraoperative complications, operative time, anastomotic leakage, postoperative complications, reoperation, readmission, postoperative

First Author, Publication Year, Country	Literature Searched, Numbers of Primary Studies Included, and Objective	Eligibility criteria	Intervention and Comparators	Clinical Outcomes
	short-term clinical outcomes of TaTME comparing with LaTME for mid and low rectal cancer	analyses, posters or conference abstracts; studies had duplicate data or repeat analysis; lack of outcome data of interest or cannot be calculated from the article data; studies on transanal extraction of other large bowel segments, such as the sigmoid or the entire colon; non-human research		hospital stay and follow-up

CRM = circumferential resection margin; DRM = distal resection margin; RCT = randomized controlled trial; SSIs = surgical site infections; TaTME = transanal total mesorectal excision; LaTME = laparoscopic total mesorectal excision.

Table 2: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country, Funding	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Bjoern 2020[19] **Denmark** **Funding source:** not reported	**Study design:** Retrospective cohort study (using existing datasets) with a prospective outcome assessment. **Setting:** Slagelse Hospital, Slagelse, Denmark **Objective:** Determine whether there is a correlation between transanal dissection and post-operative anorectal function	**Inclusion criteria:** Patients, registered in a prospective database, who had TaTME for mid- or low-rectal cancer tumours (≤ 10 cm from the anal verge) at their institution, between June 2014 and December 2017. TaTME procedures were performed by 2 surgeons. were Control group of patients were traced from a cohort of Danish Colorectal Cancer Database, who had a LaTME between February 2011 and April 2013 were included (performed by 4 surgeons). **Excluded:** Patients with anastomotic leakage. **Number of patients:** TaTME, N = 36 LaTME, N = 12 **Mean age (SD):**	**Intervention:** TaTME **Comparator:** LaTME	**Primary outcome:** internal sphincter damage (resting pressure) **Secondary outcomes:** squeeze pressure of the external anal sphincter, anal function (assessed with LARS questionnaire, which measures incontinence for flatus and stool, frequency of bowel motion, stool clustering and urgency) **Follow-up:** Follow up time from index operation to the assessment date, months [mean (SD)]: TaTME = 23.8 (9.5)

First Author, Publication Year, Country, Funding	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		TaTME = 64.4 (11.5) LaTME = 60.9 (9.9) **Sex, % male:** TaTME = 64% LaTME = 67%		Laparoscopic TME = 70.6 (9.5) P < 0.001
Bjoern 2019[18] **Denmark** **Funding source:** not reported	**Study design:** Retrospective cohort study, with a prospective outcome assessment (telephone questionnaire). **Setting:** Slagelse Hospital, Slagelse, Denmark **Objective:** Compare quality of life, bowel function, and urogenital functions between TaTME and laparoscopic TME	**Inclusion criteria:** Consecutive patients who underwent minimal invasive TME between 2010 and 2017 who are registered in a prospective database. TaTME has been the standard technique for the past 5 years. Patients who underwent LaTME were traced via the Danish Colorectal Cancer Database. **Excluded:** Patients with anastomotic leakage, or those who could not participate due to dementia or other comorbidities. **Number of patients:** TaTME, N = 49 LaTME, N = 36 **Mean age (SD):** TaTME = 64.9 (9.6) LaTME = 62.4 (10.1) **Sex, % male:** TaTME = 75% LaTME = 44% P = 0.053	**Intervention:** TaTME **Comparator:** LaTME	**Primary outcome:** Quality of life **Secondary outcomes:** bowel function (assessed with LARS questionnaire), urogenital functions **Follow-up:** ranged from 8 to 98 months post-operatively (mean follow-up 44.88 months) Time from index operation to the questionnaire date, months [mean (SD)]: TaTME = 22.7 (10.3) Laparoscopic TME = 75.1 (17.6) P < 0.001
Chen 2019[10] **Taiwan** **Funding source:** not reported	**Study design:** Retrospective cohort **Setting:** Shuang-Ho Hospital **Objective:** to investigate and analyze these three surgical techniques for the treatment of lower rectal cancer	**Inclusion criteria:** consecutive patients who underwent surgical treatment for rectal adenocarcinoma within 7 cm from the anal verge and a preoperative clinical staging of I-III between July 2008 to April 2018. **Excluded:** Patients with cancer perforation, local invasion to adjacent organs, distant metastasis, or patients who underwent abdominal perineum resection **Number of patients:** TaTME = 39 Open TME = 23	**Intervention:** TaTME **Comparator:** open TME	**Outcomes:** Operation time, blood loss, postoperative stay, conversion, complication, mortality, tumor size, CRM, harvest lymph node, local recurrence, two-year disease free survival rate, two-year overall survival rate

First Author, Publication Year, Country, Funding	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		Mean age (SD): TaTME = 62 (14.9) Open TME = 67 (10.5) **Sex, % male:** TaTME = 74.4% Open TME = 47.8%		
Perdawood 2019[20] Denmark **Funding source:** no funding received	**Study design:** Retrospective cohort study using two prospective databases **Setting:** Slagelse Hospital, Slagelse, Denmark **Objective:** determine the sites and pattern of mesorectal defects between TaTME and laparoscopic TME	**Inclusion criteria:** Patients operated between October 2010 and March 2017. The TaTME technique has been used since 2013. LaTMEwas performed prior to 2013. Patients were included if they had suboptimal TME specimen quality (intramesorectal plane and muscularis propria plane). **Excluded:** None reported. **Number of patients:** TaTME, N = 29 LaTME, N = 29 **Mean age (SD):** TaTME = 70.0 (7.1) LaTME = 70.1 (8.4) **Sex, % male:** TaTME = 76% LaTME = 59%	**Intervention:** TaTME **Comparator:** LaTME	**Primary outcome:** Quality of the mesorectum specimens (mesorectal defects) **Secondary outcomes:** operative data
Sparreboom 2019[23] **The Netherlands and Belgium** **Funding source:** not reported	**Study design:** Subgroup analysis of a prospective multicenter cohort study (the APPEAL-II study) **Setting:** 10 hospitals in the Netherlands and Belgium **Objective:** Compare post-operative morbidity between TaTME and laparoscopic TME	**Inclusion criteria:** Prospective cohort, established between August 2015 and October 2017. Patients aged 18 or older, who underwent partial mesorectal excision or TME. **Excluded:** Patient who were pregnant, or who underwent emergency procedures. **Number of patients:** 202 patients were eligible; after propensity score matching 96 patients included TaTME, N = 48 LaTME, N = 48 **Median age (IQR):** TaTME = 65.0 (56.8 to 71.0) LaTME = 64.0 (59.3 to 73.0)	**Intervention:** TaTME **Comparator:** LaTME	**Outcomes:** post-operative complications, readmissions, reoperations, conversions, mortality. **Follow-up:** occurred at the first outpatient clinic visit post-operatively Median follow up was 27 days (IQR 19 to 34 days)

First Author, Publication Year, Country, Funding	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		Sex, % male: TaTME = 68.8% LaTME = 66.7%		
Veltcamp Helbach 2019[22] **The Netherlands** **Funding source:** not reported	**Study design:** Retrospective cohort study with a prospective outcome assessment (questionnaire). **Setting:** hospital **Objective:** Compare short-to-medium term functional outcomes between TaTME and laparoscopic TME	**Inclusion criteria:** Includes two groups of patients, with tumours up to 15 cm from the anal verge, with primary anastomosis and without a current stoma. The first were patients who underwent LaTME between January 2010 and June 2012 (performed by 3 different surgeons). The second group were patients who underwent TaTME after March 2012 (performed by a single surgeon). **Excluded:** none reported. **Number of patients:** TaTME, N = 27 LaTME, N = 27 **Mean age (95% CI):** TaTME = 68.0 (64.4 to 71.6) LaTME = 62.7 (59.6 to 65.7) P = 0.040 **Sex, % male:** TaTME = 76% LaTME = 67%	**Intervention:** TaTME **Comparator:** LaTME	**Outcomes:** quality of life and anorectal function (via LARS questionnaire) **Follow-up:** questionnaires sent at least 6 months (range 6.6 to 78.0) after stoma reversal Time from index operation to the questionnaire date, months, median (range): TaTME = 20 (6.6 to 44.4) Laparoscopic TME = 59.5 (39.7 to 82.0) P = 0.000
Zeng 2019[21] **China** **Funding source:** Fundamental Research Funds for the Central Universities and Sun Yat-sen University Clinical Research 5010 Program	**Study design:** Retrospective cohort using a database generated from an RCT **Setting:** Sixth Affiliated Hospital of Sun Yat-sen University (Guangzhou, China) **Objective:** Compare the pathological results of excision specimens between TaTME and laparoscopic TME	**Inclusion criteria:** Histologically proven renal carcinoma, tumour located below the peritoneal reflection, cancer stage T3-4a, N0 or T1-4, N1-2 without threaten mesorectal fascia. Patients were enrolled between April 2016 and November 2018. All patients treated by same team. **Excluded:** could not perform sphincter preservation, tumour was invading adjacent organs, patient refused neoadjuvant therapy, recurrent cancer, previous invasive cancer with 5 years, emergency procedure, history of colorectal surgery, fecal incontinence, history of inflammatory bowel disease, or contraindications to surgery.	**Intervention:** TaTME **Comparator:** LaTME	**Outcomes:** perioperative characteristics and complications (e.g. blood loss, leakage), conversion, length of stay, 30 day post-operative mortality

First Author, Publication Year, Country, Funding	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		Number of patients: TaTME, N = 128 LaTME, N = 133 **Mean age (SD):** TaTME = 56.1 (11.2) LaTME = 56.1 (10.9) **Sex, % male:** TaTME = 64.8% LaTME = 66.9%		
Perdawood 2018[11] **Denmark** **Funding Source:** not reported	**Study Design:** case-matched retrospective study with some prospective data **Setting:** Slagelse Hospital **Objective:** To compare short-term results of TME for mid and low rectal cancer, achieved by TaTME, LaTME, and open TME approaches.	**Inclusion criteria:** TME was the operative principle, regardless of whether sphincter-saving procedure or resection and colostomy were planned; tumors 4–11 cm from the anal verge **Excluded:** extralevator abdominoperineal excision and standard abdominoperineal excision **Number of patients:** TaTME = 100 Open TME = 100 **Mean age (SD):** TaTME = 67.33 (10.81) Open TME = 68.19 (8.91) **Sex, % male:** TaTME = 72% Open TME = 72%	**Intervention:** TaTME **Comparator:** open TME	**Primary outcomes:** CRM, DRM, TME specimen quality **Secondary outcomes:** Operation time, conversion, bowel perforation, postoperative complications, anastomitic leakage, urinary dysfunction, stoma complication, hospital stay

Note: Extracted data from Chen 2019[10] and Perdawood 2018[11] relate to the comparison between TaTME versus open TME; data for TaTME versus LaTME is included in systematic reviews for Lin 2019[12] and Hajibandeh 2020[13], respectively.

CRM = circumferential resection margin; DRM = distal resection margin; LaTME = laparoscopic total mesorectal excision; RCT = randomized controlled trial; SSIs = surgical site infections; TaTME = transanal total mesorectal excision; TME = total mesorectal excision.

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[8]

Strengths	Limitations
Hajibandeh, 2020[13]	
• Well described research question and inclusion criteria • Methods were described a priori in a published protocol • The SR and MA were performed based on PRISMA statement standards • Search strategy included multiple databases, reference lists of included studies, and leading general surgical and colorectal studies • Study selection and data extraction performed in duplicate; discrepancies were resolved by a third reviewer • Methodological quality and risk of bias was assessed in duplicate using the Newcastle-Ottawa scale • Aggregate reasons for excluding studies were provided • Included studies were well described • Clear criteria were provided for the use of random-effect or fixed-effect MA • Between-study heterogeneity was assessed using Cochran's Q test, and I^2 were reported • Relevant sensitivity analyses were performed to explore heterogeneity • Publication bias was tested using funnel plots	• Exclusion criteria not directly stated • Trial registries and grey literature were not searched • 1 RCT was included • No long-term outcomes assessed • Follow-up for primary studies not reported • Reasons for excluded studies were not provided for each primary study • Conflicts of interest were not reported
Lin, 2019[12]	
• Well described research question and inclusion criteria • The SR and MA were performed based on PRISMA statement standards • Search strategy included multiple databases • Study selection and data extraction performed in duplicate • Included studies were well described • Aggregate reasons for excluding studies were provided • Unclear how random-effect modelling was selected • Between-study heterogeneity was assessed using Cochran's Q test, and I^2 were reported • Quality of studies was assessed using the Newcastle-Ottawa scale • Publication bias was tested using funnel plots	• Unclear if methods were established a priori as no pre-published protocol was referenced • Trial registries and grey literature were not searched • Unclear how study selection and data extraction disagreements were resolved • Reasons for excluded studies were not provided for each primary study • No RCTs included • No long-term outcomes assessed • Follow-up for primary studies not reported • Conflicts of interest were not reported
Hu, 2018[15]	
• Well described research question and inclusion criteria	• Unclear if methods were established a priori as no pre-published protocol was referenced

Strengths	Limitations
• The SR and MA were performed based on PRISMA statement standards • Search strategy included multiple databases in English and Chinese • Study selection, data extraction and risk of bias assessment performed in duplicate; disagreements were resolved by discussion • Included studies were well described • Aggregate reasons for excluding studies were provided • Clear criteria were provided for the use of random-effect or fixed-effect MA • Quality of matched case-control studies was assessed using the Newcastle-Ottawa scale • Quality of RCTs was evaluated using Cochrane Library Handbook 5.1.0. • Publication bias was tested using funnel plots • Between-study heterogeneity was assessed using Cochran's Q test, and I^2 were reported • No conflict of interest	• Reasons for excluded studies were not provided for each primary study • Trial registries and grey literature were not searched • No long-term outcomes assessed • Follow-up for primary studies not reported
Ma, 2016[16]	
• Well described research question and inclusion criteria • The SR and MA were performed based on PRISMA statement standards • Search strategy included multiple databases • Study selection and data extraction performed in duplicate; disagreements were resolved by discussion • Included studies were well described • Aggregate reasons for excluding studies were provided • Clear criteria were provided for the use of random-effect or fixed-effect MA • Quality of studies was assessed in duplicate using the Newcastle-Ottawa scale • Between-study heterogeneity was assessed using Cochran's Q test, and I^2 were reported • MA were performed using random-effects or fixed-effect modelling as appropriate for analysis • Publication bias was assessed using funnel plots • No conflict of interest	• Unclear if methods were established a priori as no pre-published protocol was referenced • Reasons for excluded studies were not provided for each primary study • Trial registries and grey literature were not searched • 1 RCT was included • No long-term outcomes assessed • Follow-up for primary studies not reported •
Xu, 2016[17]	
• Well described research question and inclusion criteria • Search strategy included multiple databases • Study selection and data extraction performed in • duplicate; disagreements were resolved by consensus • Included studies were well described, follow-up for primary studies was provided when available • Aggregate reasons for excluding studies were provided	• Unclear if SR and MA were performed based on PRISMA statement standards • Unclear if methods were established a priori as no pre-published protocol was referenced • Reasons for excluded studies were not provided for each primary study • Trial registries and grey literature were not searched • No RCTs included • No long-term outcomes assessed

Strengths	Limitations
• Clear criteria were provided for the use of random-effect or fixed-effect MA • Quality was assessed using the Newcastle-Ottawa scale • Between-study heterogeneity was assessed using Cochran's Q test, and I^2 were reported • Publication bias was assessed using funnel plots • No conflict of interest	

RCT = randomized control trial; MA = meta-analysis; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SR = systematic review.

Table 4: Strengths and Limitations of Clinical Studies using the Downs and Black Checklist[9]

Strengths	Limitations
Bjoern, 2020[19]	
• The objectives, patient characteristics, interventions, controls, and outcomes were well described • Baseline characteristics were generally well balanced with a few exceptions • No loss to follow up due to retrospective cohort design • Appropriate statistical analysis • No conflict of interest	• The study took place at different times for each group (TaTME = June 2014 to December 2017; LaTME = February 2011 to April 2013) this was reflected in significantly longer follow-up time in the LaTME group • Significantly fewer lymph node-positive patients in the TaTME group • The participation rate varied between groups (TaTME 73%, LaTME = 50%) • Unclear if analysists were blinded • Unclear if power calculation was used to determine sample size • TaTME performed by two surgeons, LaTME performed by four surgeons
Bjoern 2019[18]	
• The objectives, patient characteristics, interventions, controls, and outcomes were well described • Baseline characteristics were generally well balanced with a few exceptions • No loss to follow up due to retrospective cohort design • Telephone interviewers were blinded • Appropriate statistical analysis • No conflict of interest	• Significant difference in mean follow-up between groups, longer follow-up time associated with LaTME • Significantly fewer lymph node-positive patients in the TaTME group • Unclear if analysts were blinded • Unclear if power calculation was used to determine sample size • TaTME performed by one surgeon, LaTME performed by more than one surgeon
Chen 2019[10]	
• The objectives, patient characteristics, interventions, controls, and outcomes were well described • Baseline characteristics were generally well balanced with a few exceptions • No loss to follow up due to retrospective cohort design • Appropriate statistical analysis • No conflict of interest	• Significant difference in mean follow-up between groups, longer follow-up time associated with open TME • Fewer patients with stage I cancer in the open TME group • TaTME performed by one surgeon, open TME performed by several surgeons • Unclear if analysts were blinded

Strengths	Limitations
	• Unclear if power calculation was used to determine sample size
Perdawood, 2019[20]	
• The objectives, patient characteristics, interventions, controls, and outcomes were well described • Appropriate statistical analysis • No conflict of interest	• Follow-up time was not reported • Unclear if analysts were blinded • Unclear if power calculation was used to determine sample size
Sparreboom, 2019[23]	
• The objectives, patient characteristics, interventions, controls, and outcomes were well described • After matching baseline characteristics were well balanced • Appropriate statistical analysis	• Prospective study design • Follow-up time was not reported by treatment arm • Unclear if analysts were blinded • Subgroup analysis; no power calculation to determine sample size for subgroup • Different types of TME procedures were used (e.g., single-port, multi-port)
Veltcamp Helbach 2019[22]	
• The objectives, patient characteristics, interventions, controls, and outcomes were well described • Baseline characteristics were generally well balanced with a few exceptions • No loss to follow up due to retrospective cohort design • Appropriate statistical analysis • Conflict of interest reported	• TaTME performed by one surgeon, LaTME performed by three surgeons • Patients in the TaTME arm were significantly older than those in the LaTME arm • Significant difference in mean follow-up between groups, longer follow-up time associated with LaTME • Unclear if analysts were blinded • Unclear if power calculation was used to determine sample size
Zeng 2019[21]	
• The objectives, patient characteristics, interventions, controls, and outcomes were well described • Baseline characteristics were well balanced when reported • No loss to follow up due to retrospective cohort design • Appropriate statistical analysis • No conflict of interest	• Follow-up time not reported • Unclear if analysts were blinded • Unclear if power calculation was used to determine sample size
Perdawood 2018[11]	
• The objectives, patient characteristics, interventions, controls, and outcomes were well described • Baseline characteristics were well balanced when reported • No loss to follow up due to retrospective cohort design • Appropriate statistical analysis • No conflict of interest	• Follow-up time not reported • Unclear if analysts were blinded • Unclear if power calculation was used to determine sample size • Number and experience of surgeons is unclear

LaTME = laparoscopic total mesorectal excision; TaTME = transanal total mesorectal excision; TME = total mesorectal excision; MA = meta-analysis.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 5: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Hajibandeh, 2020[13]	
Primary Outcomes: **Intraoperative complications:** • 11 studies • No statistically significant difference between TaTME and LaTME (OR 1.18; 95% CI 0.69 to 2.01, P = 0.54) • Low between-study heterogeneity (I^2 = 0%, P = 0.66) **Postoperative complications:** • 17 studies • No statistically significant difference between TaTME and LaTME (OR 0.89; 95% CI 0.74 to 1.08, P = 0.24) • Moderate between-study heterogeneity (I^2 = 43%, P = 0.03) **Anastomotic leak:** • 16 studies • No statistically significant difference between TaTME and LaTME (OR 0.88; 95% CI 0.64 to 1.20, P = 0.42). • Low between-study heterogeneity (I^2 = 0%, P = 0.61) **SSIs:** • 6 studies • No statistically significant difference between TaTME and LaTME (OR 0.64; 95% CI 0.30 to 1.38, P = 0.26) • Low between-study heterogeneity (I^2 = 0%, P = 0.73) **Primary Oncology Outcomes:** **Completeness of mesorectal excision:** • 14 studies • No statistically significant difference between TaTME and LaTME (OR 1.43; 95% CI 0.84 to 2.46, P = 0.19) • Moderate between-study heterogeneity (I^2 = 58%, P = 0.003) **CRM:** • 9 studies • No statistically significant difference between TaTME and LaTME (MD 0.36; 95% CI − 0.91 to 1.63, P = 0.58) • Significant between-study heterogeneity (I^2 = 76%, P < 0.0001) **Positive CRM:** • 14 studies • TaTME was associated with a significantly lower rate of positive CRM • (OR 0.67; 95% CI 0.45 to 0.98, P = 0.04) • Low between-study heterogeneity (I^2 = 0%, P = 0.76) **DRM:** • 13 studies • No statistically significant difference between TaTME and LaTME (MD 1.87; 95% CI − 0.75 to 4.49, P = 0.16)	*"…TaTME may be associated with significantly higher rate of R0 resection, lower rate of positive CRM, higher rate of harvested lymph nodes, and lower number of conversion to an open procedure compared with LaTME in management of middle and low rectal cancer. Moreover, it may carry similar risk of perioperative morbidity and ability to resect distally and circumferentially."*

Main Study Findings	Authors' Conclusion
• Moderate between-study heterogeneity (I^2 = 74%, P < 0.0001) **<u>Secondary Outcomes:</u>** **Conversion to open:** • 15 studies • TaTME was associated with a significantly lower rate of conversion to an open procedure (OR 0.17; 95% CI 0.10 to 0.29, P < 0.00001) • Low between-study heterogeneity (I^2 = 15%, P = 0.30) **Length of hospital stay:** • No data	
Lin, 2019[12]	
<u>Intraoperative Outcomes:</u> **Conversion rate:** • 10 studies • No statistically significant difference between TaTME and LaTME (OR 0.77; 95% CI 0.22 to 2.75, P = 0.69 **Blood loss:** • 5 studies • No statistically significant difference between TaTME and LaTME (MD 2.82; 95% CI -26.26 to 31.91, P = 0.85 **Intraoperative complications:** • 8 studies • No statistically significant difference between TaTME and LaTME (OR 1.15; 95% CI 0.57 to 2.33, P = 0.70 **<u>Postoperative Outcomes:</u>** **Overall postoperative complication:** • 10 studies • No statistically significant difference between TaTME and LaTME (OR 0.94; 95% CI 0.67 to 1.3, P = 0.74 **Anastomotic leakage:** • 9 studies • No statistically significant difference between TaTME and LaTME (OR 0.84; 95% CI 0.47 to 1.5, P = 0.61 **Ileus:** • 8 studies • No statistically significant difference between TaTME and LaTME (OR 1.15; 95% CI 0.57 to 2.33, P = 0.70 **Urinary morbidity:** • 4 studies • No statistically significant difference between TaTME and LaTME (OR 0.65; 95% CI 0.23 to 1.87, P = 0.43	*"Our results showed no significant difference between TaTME and LaTME in overall intraoperative complications, postoperative outcomes, oncological outcomes or local recurrence. We hope that our findings can illustrate the safety and feasibility of TaTME, and promote its application in middle and low rectal cancer." (p.356)* *"TaTME offers a safe and feasible alternative to LaTME although the clinicopathological features were not superior to LaTME in this study." (p.359)*

Main Study Findings	Authors' Conclusion
Readmission: • 6 studies • The TaTME group had non-significantly better postoperative outcomes than the LaTME group (OR 0.52; 95% CI 0.25 to 1.07, P = 0.08 **Length of hospital stay:** • 11 studies • The TaTME group had non-significantly better postoperative outcomes than the LaTME group (MD -0.89; 95% CI -1.92 to 0.13, P = 0.09 **Oncology Outcomes:** **CRM:** • 6 studies • No statistically significant difference between TaTME and LaTME (MD 1.14; 95% CI -1.18 to 3.46, P = 0.33 **Positive CRM:** • 11 studies • No statistically significant difference between TaTME and LaTME (OR 0.70; 95% CI 0.34 to 1.42, P = 0.32 **DRM:** • 8 studies • No statistically significant difference between TaTME and LaTME (MD 2.83; 95% CI -2.11 to 7.77, P = 0.26 **Positive DRM:** • 5 studies • No statistically significant difference between TaTME and LaTME (OR 0.62; 95% CI 0.16 to 2.44, P = 0.51 **Quality of mesorectum:** • 10 studies • No statistically significant difference between TaTME and LaTME (OR 0.76; 95% CI -0.97 to 2.48, P = 0.39 **Local recurrence:** • 4 studies • No statistically significant difference between TaTME and LaTME (OR 1.03; 95% CI 0.27 to 3.93, P = 0.96	
Hu, 2018[15]	
<u>Oncological Outcomes:</u> **Mactosocopic quality of mesoretum:** • 5 studies • Macroscopic quality of the mesorectum was better in the TaTME group than in the LaTME group (OR = 1.93, 95% CI = 1.09 to 3.42, P = 0.02) • Between-study heterogeneity: I2 = 0%, P = 0.47 **CRM:** • 8 studies • A longer circumferential resection margin was identified in the TaTME group (WMD = 0.95, 95% CI = 0.60 to 1.31, P = 0.001) • Between-study heterogeneity: I^2 = 0%, P = 0.48	*"TaTME was associated with a reduction in the positive CRM rate, TaTME thus could achieve complete tumor resection and improve long-term survival of patients with mid- and low-rectal cancer." (p.7)*

Main Study Findings	Authors' Conclusion
Positive CRM: • 9 studies • A lower positive circumferential resection margin was identified in the TaTME group (OR = 0.43, 95% CI = 0.22 to 0.82, P = 0.01) • Between-study heterogeneity: I^2 = 0%, P = 0.90 **DRM:** • 8 studies • No statistically significant difference between TaTME and LaTME (WMD = 2.12, 95% CI = -2.26 to 6.51, P = 0.34) • Between-study heterogeneity: I^2 = 79%, P = 0.00 **Positive DRM:** • 5 studies • No statistically significant difference between TaTME and LaTME (OR = 1.14, 95% CI = 0.19 to 6.75, P = 0.89) • Between-study heterogeneity: I^2 = 37%, P = 0.19 **<u>Perioperative Outcomes:</u>** **Conversion:** • 9 studies • A lower rate of conversion was identified in the TaTME group (OR = 0.27, 95% CI = 0.12 to 0.59, P=0.001) • Between-study heterogeneity: I^2 = 0%, P = 0.77 **Intraoperative complications:** • 5 studies • No statistically significant difference between TaTME and LaTME (OR = 0.85, 95%CI = -2.97 to -4.66, P=0.66) **Blood loss:** • 3 studies • No statistically significant difference between TaTME and LaTME (MD = -28.86, 95%CI = -56.64 to 2.91, P=0.08) **<u>Postoperative Outcomes:</u>** **Ileus:** • 6 studies • No statistically significant difference between TaTME and LaTME (OR = 0.91, 95% CI = 0.46 to 1.78, P = 0.78) **Readmission:** • 7 studies • No statistically significant difference between TaTME and LaTME (OR = 0.57, 95% CI = 0.31 to 1.03, P = 0.06) **Hospital Stay** • 8 studies • No statistically significant difference between TaTME and LaTME (MD = -0.64, 95% CI = -1.37 to 0.10, P = 0.09)	

Main Study Findings	Authors' Conclusion
Anastomic leakage • 7 studies • No statistically significant difference between TaTME and LaTME (OR = 0.79, 95% CI = 0.45 to 1.38, P = 0.40) **Postoperative complications** • 6 studies • No statistically significant difference between TaTME and LaTME (OR = 0.75, 95% CI = 0.51 to 1.09, P = 0.13)	
Ma, 2016[16]	
<u>Oncological Outcomes:</u> **Mactosocopic quality of mesoretum:** • 5 studies • The complete grade for the quality of the mesorectum was significantly higher for TaTME than for LaTME (OR = 1.75, 95% CI = 1.02 to 3.01, P = 0.04) • Between-study heterogeneity: I^2 = 0%, P = 0.46 **CRM:** • 7 studies excluding patients with complete remission • The TaTME group showed a significantly greater CRM than the LaTME group (WMD= 0.96, 95% CI = 0.60 to 1.31, P <0.01) • Between-study heterogeneity: I^2 = 9%, P = 0.36 **Positive CRM:** • 6 studies • Significantly lower number of patients in the TaTME group had a positive CRM (OR = 0.39, 95% CI = 0.17 to 0.86, P=0.02) • Between-study heterogeneity: I^2 = 81%, P< 0.0001 **DRM:** • 7 studies excluding patients with complete remission • Comparable between TaTME and LaTME (WMD= 2.71, 95% CI = -1.97to 7.39, P = 0.26) • Between-study heterogeneity: I^2 = 9%, P = 0.36 **Positive DRM:** • 3 studies • Comparable between TaTME and LaTME (OR = 1.65, 95% CI = 0.17 to 16.40, P=0.67) • Between-study heterogeneity: I^2 = 53%, P = 0.12 **<u>Perioperative outcomes:</u>** **Conversion (to open):** • 6 studies • The TaTME group showed a significantly lower conversion rate (WMD = –23.45, 95% CI = –37.43 to –9.46) • Between-study heterogeneity: I^2 = 0%, P = 0.79 **Hospital stay:** • 6 studies	*"… TaTME can achieve comparable technical success in comparison with LaTME, in the treatment of rectal cancer." (p.11)*

Main Study Findings	Authors' Conclusion
• Comparable between TaTME and LaTME (WMD = –1.18, 95% CI = –2.94 to 0.59) **Intraoperative complications:** • 4 studies • No statistically significant difference between TaTME and LaTME (OR = 0.94, 95% CI = 0.30 to 3.01, P = 0.92) **<u>Postoperative outcomes:</u>** **Postoperative complications:** • 6 studies • The TaTME group showed a significantly lower rate of postoperative complications than the LaTME group (OR = 0.65, 95% CI = 0.45 to 0.95, P = 0.03) • Between-study heterogeneity: I^2 = 23%, P = 0.26 **Anastomotic leakage:** • 6 studies • Comparable between TaTME and LaTME (OR = 0.78, 95% CI = 0.44 to 1.40, P = 0.41) **Ileus:** • 6 studies • Comparable between TaTME and LaTME (OR = 1.00, 95% CI = 0.45 to 2.19, P = 1.00) **Urinary morbidity:** • 6 studies • Comparable between TaTME and LaTME (OR = 0.48, 95% CI = 0.22 to 1.03) **Readmission:** • 4 studies • Fewer patients after TaTME would require readmission (not statistically significant) (OR = 0.52, 95% CI = 0.24 to 1.10, P = 0.09) • Between-study heterogeneity: I^2 = 0%, P = 0.57	
Xu, 2016[17]	
<u>Operative Outcomes:</u> **Quality of TME:** • 4 studies • TaTME showed a significantly higher complete quality of TME rate compared to LaTME (OR 0.34, 95% CI 0.12 to 0.93, P = 0.04) • I^2 = 0% **CRM:** • 5 studies • TaTME showed a longer CRM than LaTME (WMD 0.95; 95% CI 0.61 to 1.29; • I^2 = 5% **Positive CRM:** • 6 studies	"*Compared with LaTME, TaTME is a feasible and safe approach for patients with mid and low rectal cancer. In addition, TaTME showed a better short-term clinical outcomes, such as a longer CRM, lower risk of positive CRM, higher complete quality of TME rate, and shorter operative duration." (p.1849)*

Main Study Findings	Authors' Conclusion
• TaTME showed a lower rate of positive CRM than LaTME (OR 0.34; 95% CI 0.12 to 0.93) • I^2 = 0% **DRM:** • 6 studies • No statistically significant difference between TaTME and LaTME (WMD 0.43; 95% CI -0.11 to 0.97; • I^2 = 74% **Blood loss:** • 3 studies • No statistically significant difference between TaTME and LaTME (WMD -64.26; 95% CI -137.39 to 8.88) • I^2 = 67% **Intraoperative complications:** • 4 studies • No statistically significant difference between TaTME and LaTME (OR 0.94; 95% CI 0.30 to 3.01) • I^2 = 0% **Conversion:** • 6 studies • No statistically significant difference between TaTME and LaTME (OR 0.75; 95% CI 0.31 to 1.78) • I^2 = 9% **<u>Postoperative Outcomes:</u>** **Anastomotic leakage:** • 5 studies • No statistically significant difference between TaTME and LaTME (OR 0.81; 95% CI 0.42 to 1.56) • I^2 = 0% **Postoperative complications:** • 6 studies • No statistically significant difference between TaTME and LaTME (MD 0.43; 95% CI -0.11 to 0.97) • I^2 = 74% **Readmission:** • 6 studies • No statistically significant difference between TaTME and LaTME (OR 0.75; 95% CI 0.31 to 1.78) • I^2 = 9% **Postoperative hospital stay:** • 3 studies • No statistically significant difference between TaTME and LaTME (MD -64.26; 95% CI -137.39 to 8.88) • I^2 = 67%	

CI = confidence interval; CI = confidence interval; CRM = circumferential resection margin; DRM = distal resection margin; MD = mean difference; OR = odds ratio; SSIs = surgical site infections; TaTME = transanal total mesorectal excision; LaTME = laparoscopic total mesorectal excision; WMD = weighted mean difference

Table 6: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Bjoern 2020[19]	
Total LARS score, mean (SD) TaTME = 29.50 (8.21) vs. LaTME= 28.05 (9.61), P = 0.622 **Resting pressure, mmHg, [mean (SD)]** [measure of internal sphincter damage] TaTME = 36.44 (18.51) vs. LaTME= 36.58 (13.32), P = 0.981 **Patients within normal range of resting pressure, %** TaTME = 33.3% vs. LaTME=58.3%, P = 0.176 **Squeeze pressure of external anal sphincter, mmHg, [mean (SD)]** TaTME = 125.00 (66.14) vs. LaTME= 111.83 (51.11), P = 0.533 **Patients within normal range of squeeze pressure, %** TaTME = 58.3% vs. LaTME=50%, P = 0.614	*"In this data set, there was a comparable total LARS score (severity) in the two groups and there were no significant differences in the single parameters regarding anorectal function" (p. 233)* *"Based on our current data set we suggest that perioperative damage to the anal sphincter seems unlikely to be increased with the transanal approach since incontinence for flatus and stools is comparable in TaTME and LaTMEpatients." (p. 235)*
Bjoern 2019[18]	
Quality of life, EORTC QLQ-C30, global health status, mean TaTME = 77.72 vs. LaTME= 79.86, P = 0.625 **Total LARS score, mean (SD)** TaTME = 26.18 (10.32) vs. LaTME= 20.61 (14.51), P = 0.054 **IPSS score, mean (SD)** TaTME = 6.73 (7.42) vs. LaTME= 10.05 (8.15), P = 0.060	*"Quality of life/the global health status was comparable in the two groups. No significant differences were found on the functional scales including physical, role, cognitive, and social functioning. However, the reported emotional functioning was significantly in favor of LaTME, as was symptoms of diarrhea. The remaining symptom scales concerning fatigue, nausea, pain, dyspnea, insomnia, and constipation as well as financial difficulties were comparable." (p.1625)* *"Symptoms related to anorectal dysfunction were reported in both groups, and no significant differences regarding the overall severity, as reflected by the three categories in the LARS score, were found. Mean of total LARS score was in disfavor of TaTME, yet this did not reach statistical significance." (p. 1625)* *"The urinary function was comparable between the male subgroups on all severity levels." (p. 1626)* *"We find that anorectal dysfunction may occur after TME, regardless of surgical technique (transanal or laparoscopic), and the overall quality of life is comparable between the groups." (p. 1629)*

Main Study Findings	Authors' Conclusion
Chen 2019[10]	
Post-operative hospital stay, mean days (SD): TaTME = 9.2 (2.7) vs. Open TME = 9.4 (2.4), P = not reported **Blood Loss, ml (SD):** TaTME = 63 (102) vs. Open TME = 113 (129), P = 0.01 **Peri-operative Complication, n (%):** TaTME = 4 (10.2) vs. Open TME = 2 (8.7), P = not reported **Anastomotic leakage, n:** TaTME = 1 vs. Open TME = 0, P = not reported **Ileus** TaTME = 1 vs. Open TME = 1, P = not reported **Urinary dysfuntion or discharge** TaTME = 2 vs. Open TME = 1, P = not reported **Mortality (post operation 30 days), n:** TaTME = 0 vs. Open TME = 0, P = 1.00 **Distal margin (cm)** TaTME = 1.3 (1.4) vs. Open TME = 1.6 (0.9), P = not reported **CRM (mm),** <1 mm: TaTME = 0 vs. Open TME = 3 ≥ 1 mm: TaTME = 39 vs. Open TME = 20 P < 0.01 **Local recurrence, n (%)** TaTME =0 vs. Open TME = 2 (8.7%), P = not reported **Two year disease free survival rate** TaTME = 0.90 vs. Open TME = 0.65 , P = 0.01	*"TaTME provides surgeons with a novel and effective method to treat lower rectal cancer. In the short-term outcomes, TaTME achieved better pathological results and disease free survival than OpTME" (p.675)*
Perdawood 2019[20]	
Conversion to open surgery, n (%) TaTME = 0 vs. LaTME= 2 (6.9), P = 0.491 **Circumferential resection margin distance, mm, mean (SD)** TaTME = 10.48 (8.05) vs. LaTME= 8 (6.52), P = 0.202 **Ratio of defects under the peritoneal reflection, n (%)** TaTME = 17 (58.6) vs. LaTME= 24 (82.7), P = 0.043 **DRM involvement, n (%)** TaTME = 0 vs. Laparoscopic TME = 1 (3.4), P = 1.000 **DRM distance, mm, mean (SD)** TaTME = 33.45 (14.50) vs. Laparoscopic TME = 25.41 (15.78), P = 0.048	*"Operative data showed a statistically significant difference in operative time, blood loss, and DRM involvement in favor of TaTME group" (p. 51)* *"When the distribution of the defects was compared according to potential locations (above, below, or both), the difference did not reach statistical significance. However, the difference reached statistical significance when categorizing the groups according to whether or not a specimen had a defect below the peritoneal reflection. Thus, the ratio of the defects below the peritoneal reflection was higher in the LaTME group." (p. 51)*

Main Study Findings	Authors' Conclusion
Blood loss, mL, mean (SD) TaTME = 73.79 (56.23) vs. Laparoscopic TME = 188.97 (283.63), P = 0.036 **Perforation, n (%)** TaTME = 3 (10.3) vs. Laparoscopic TME = 4 (13.8), P = 1.000 **CRM involvement, n (%)** TaTME = 1 (3.4) vs. Laparoscopic TME = 3 (10.3), P = 0.306	*"When the sites of defects are analyzed according to the anatomical location (above or below the peritoneal reflection), the ratio of defects below the peritoneal reflection is lower in the TaTME group compared to the LaTME group. Thus, TaTME has the potential to improve rectal cancer surgery through improvement in the quality of dissection in the lower rectum." (p. 53)*
Sparreboom 2019[23]	
Conversion, n (%) TaTME = 0 (0) vs. LaTME= 5 (10.4), P = 0.056 **Hospital stay, days, median (IQR)** TaTME = 8.0 (6.0 to 13.5) vs. LaTME= 7.5 (5.0 to 13.8), P = 0.596 **Anastomotic leakage, n (%)** TaTME = 10 (20.8) vs. LaTME= 9 (18.8), P = 0.798 **Wound infection, n (%)** TaTME = 2 (4.2) vs. LaTME= 1 (2.1), P = 1.000 **Comprehensive complication index, median (IQR)** TaTME = 14.8 (0.0 to 22.6) vs. LaTME= 4.4 (0.0 to 22.6), P = 0.602 **Readmission, n (%)** TaTME = 10 (20.8) vs. LaTME= 5 (10.4), P = 0.160 **Reoperation, n (%)** TaTME = 8 (16.7) vs. LaTME= 7 (14.6), P = 0.779 **Mortality, n (%)** TaTME = 0 (0) vs. LaTME= 1 (2.1), P = 1.000	*"TaTME was not converted to laparotomy whilst surgery in five patients undergoing LaTME was converted to laparotomy. Reasons for conversion were adhesions, obesity, bleeding and insufficient bowel length for stoma creation." (p. 769)* *"No statistically significant differences were observed for hospital stay, anastomotic leakage, ileus, cardiopulmonary complications, wound infections, Clavien–Dindo classification, comprehensive complication index, readmissions, reoperations and mortality" (p. 769)* *"Our results suggest that TaTME is a safe and feasible approach for rectal cancer resection and has similar postoperative morbidity to laparoscopic TME." (p. 770)*
Veltcamp Helbach 2019[22]	
Quality of life, EQ-5D-3L, overall score, mean (95% CI) TaTME = 88.1 (83.1 to 93.1) vs. LaTME= 92.8 (88.2 to 97.4), P = 0.159 **Quality of life, EQ-5D-3L, global health status (by visual analog scale), mean (95% CI)** TaTME = 75.6 (69.9 to 81.3) vs. LaTME= 79.1 (72.8 to 85.3), P = 0.400 **Quality of life, EORTC QLQ-C30, global health status, mean** TaTME = 79.6 vs. LaTME= 83.6, P = 0.208 **Total LARS score, mean (95% CI)** TaTME = 27.7 (22.3 to 32.8) vs. LaTME= 24.0 (19.9 to 32.8), P = 0.267 **IPSS score, mean (95% CI)** TaTME = 8 (4.2 to 11.8) vs. LaTME= 6.7 (3.6 to 11.8), P = 0.582	*"Quality of life measures did not reveal any significant differences" (p. 81)* *"Although patients in both groups reported LARS, no significant difference in the severity was identified between the two groups." (p. 83)* *"No significant differences were seen when comparing IPSS scores per subgroup: (p. 83)* *"The short-to-medium term functional outcome data reported in our study, including anorectal function and quality of life, did not reveal any major differences between the transanal and LaTME groups" (p. 83)*

Main Study Findings	Authors' Conclusion
Zeng 2019[21]	
Conversion to an open approach, n (%) TaTME = 0 (0) vs. LaTME= 0 (0), P = 1 **Length of stay in hospital, days, mean (SD)** TaTME = 10.8 (6.6) vs. LaTME= 11.2 (6.0), P = 0.607 **Post-operative complication, n (%)** TaTME = 13 (10.2) vs. LaTME= 19 (14.3), P = 0.309 **Anastomotic leakage, n (%)** TaTME = 7 (5.4) vs. LaTME= 5 (3.8), P = not reported **Blood loss, ml, mean (SD)** TaTME = 69.4 (53.9) vs. Laparoscopic TME = 79.2 (66.3), P = 0.374 **Secondary operation due to complication, n (%)** TaTME = 2 (15.3) vs. LaTME= 7 (36.8), P = 0.353 **Mortality rate (post-surgery 30 days)** TaTME = 0 vs. LaTME= 0, P = 1 **Mesorecatal resection quality, n (%)** **Complete:** TaTME = 121 (94.5) vs. LaTME= 119 (89.5) **Nearly complete:** TaTME = 7 (5.5) vs. LaTME= 14 (10.5) **Incomplete:** TaTME = 0 (0) vs. LaTME= 0 (0) P = 0.173 **CRM status, n (%)** **Positive:** TaTME = 2 (1.6) vs. LaTME= 2 (1.5) **Negative:** TaTME = 126 (98.4) vs. LaTME= 131 (98.5) P = 0.674 **Length between tumor and DRM, cm, mean (SD)** TaTME = 1.4 (1.1) vs. Laparoscopic TME = 1.3 (0.9), P = 0.745 **DRM status, n (%)** **Positive:** TaTME = 0 (0) vs. Laparoscopic TME = 2 (1.5) **Negative:** TaTME = 128 (100) vs. Laparoscopic TME = 131 (98.5) P = 0.498	*"The quality of mesorectal specimen was complete or near complete for all patients." (p. 4)* *"This study showed that TaTME is a safe and feasible method to mid-low rectal cancer surgery, and it can achieve comparable pathological results compared to laparaoscopic TME. We consider that TaTME has potential to improve the quality of the mesorectal specimen. But more studies are needed to confirm the potential advantages of TaTME. (p. 6)*
Perdawood 2018[11]	
Specimen quality, n: **Complete:** TaTME = 58 vs. open TME = 68 **Nearly complete:** TaTME = 28 vs. open TME = 15 **Incomplete:** TaTME = 14 vs. open TME = 17 P = 0.082 **CRM involvement, n:** TaTME = 7 vs. open TME = 10, P = 0.447 **CRM, mean mm (SD):** TaTME = 8.99 (7.21) vs. open TME = 9.57 (7.49), P = not reported **DRM involvement, n:** TaTME = 0 vs. open TME = 1, P = not reported	*"TaTME had, in our hands, some obvious benefits over other approaches in terms of the operation time, blood loss, and higher rates of sphincter-saving procedures. However, the pathological results were not significantly superior to LaTME and OpTME. The procedure is, however, feasible and safe." (P.2320)*

Main Study Findings	Authors' Conclusion
DRM, mean mm (SD): TaTME = 25.18 (14.34) vs. open TME = 30.83 (21.91), P = 0.065 **Intraoperative complications:** TaTME = 13 vs. open TME = 16, P = not reported **Bowel perforation:** TaTME = 2 vs. open TME = 8, P = not reported **Bleeding:** TaTME = 8 vs. open TME = 6, P = not reported **Anastomotic leakage, n (%):** TaTME = 6 (9.5%) vs. open TME = 17 (25.85%), P = 0.016 **Urinary dysfunction, n**: TaTME = 19 vs. open TME = 22, P =0.517 **Wound infection, n:** TaTME = 6 vs. open TME = 10, P = not reported **Hospital stay, mean days (SD):** TaTME = 8.63 (6.20) vs. open TME = 15.51 (11.14), P < 0.001 **Readmission, n:** TaTME = 14 vs. open TME = 20, P =0.879 **30-days mortality, n:** TaTME = 2 vs. open TME = 2, P = not reported	

Note: extracted data from Chen 2019[10] and Perdawood 2018[11] relate to the comparison between TaTME versus open TME; data for TaTME versus LaTME is included in systematic reviews for Lin 2019[12] and Hajibandeh 2020[13], respectively.

CI = confidence interval; CRM = circumferential resection margin; DRM = distal resection margin; IPSS = International Prostate Syndrome Score; LARS = Low Anterior Resection Syndrome; MD = mean difference; OR = odds ratio; SD = standard deviation; SSIs = surgical site infections; TaTME = transanal total mesorectal excision; LaTME = laparoscopic total mesorectal excision; WMD = weighted mean difference.

Appendix 5: Overlap between Included Systematic Reviews

Table 7: Primary Study Overlap between Included Systematic Reviews

Primary Study Citation	Systematic Review Citation				
	Hajibandeh, 2020[13]	Lin, 2019[12]	Hu, 2018[15]	Ma, 2016[16]	Xu, 2016[17]
Denost, 2014			X	X	
Hevia, 2014				X	
Simone, 2014					X
Velthius, 2014	X		X	X	
De'Angelis, 2015	X	X	X	X	X
Fernandez-Hevia, 2015	X	X	X		X
Kanso, 2015			X	X	
Chen CC, 2016	X	X	X	X	X
Chouillard, 2016	X	X	X		X
D'Ambrosio, 2016			X		
Marks, 2016	X		X		
Perdawood, 2016	X		X	X	X
Pontallier, 2016	X		X		
Rasulov, 2016	X	X	X		X
Chang, 2017	X	X			
Lelong, 2017	X	X	X		
Chen YT, 2018		X			
Mege, 2018	X	X			
Perdawood, 2018	X				
Persiani, 2018	X	X			
Roodbeen, 2018	X	X			
Rubinkiewicz, 2018	X	X			
Sheng, 2018					
Veltcamp, 2018	X				
Detering, 2019	X				